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CORRESPONDENCE

The Anrep effect in septic shock: a mechanism of cardiac adaptation

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Editor—Septic shock, marked by vasoplegic hypotension, impaired tissue perfusion, and myocardial dysfunction, remains a major challenge in intensive care.[1] Norepinephrine (NE) is the first-line vasopressor recommended for managing hypotension because of its ability to increase systemic vascular resistance and restore organ perfusion.[1] NE acts primarily via α1-adrenergic receptors in vascular smooth muscle, driving vasoconstriction and increased afterload. Secondary β1-and potentially α1-mediated myocardial effects provide additional support by enhancing myocardial contractility.[2,3] Despite widespread clinical application, the precise mechanisms by which NE modulates stroke volume (SV) and cardiac function in septic shock remain only partially understood. Proposed mechanisms include improved coronary perfusion, enhanced ventricular–arterial coupling (VAC), increased stressed blood volume, and intrinsic cardiac responses such as the Anrep effect.[2] However, the relative contributions of these mechanisms to the haemodynamic effects of NE remain under debate.

Ventricular–arterial coupling and the role of norepinephrine

Precise (non)invasive pressure–volume measurements are not routinely performed in the operating room, and even in patients with septic shock standard monitoring parameters such as cardiac output, SV, afterload, and wedge pressure (as a surrogate for preload) lack the granularity needed to isolate the mechanisms influencing cardiac function.[4] For instance, SV can be affected by preload (e.g. via the Frank–Starling mechanism) or contractility (e.g. through adrenergic stimulation or the Anrep effect). Most studies on vasopressor agents do not differentiate these contributions, and such detailed assessments are rare. Recently, Zhou and colleagues[5] provided a comprehensive echocardiography-derived pressure–volume analysis in patients with septic shock treated with NE, assessing VAC, expressed as the ratio of arterial elastance (Ea) to left ventricular end-systolic elastance (Ees). NE administration increased both Ea (reflecting afterload) and Ees (indicating myocardial contractility), while prolonging systolic duration (Ttot-s), particularly in patients identified as 'SV responders'.[5] These findings offer more than a simple prediction of patient responses to NE. They provide a meaningful framework for understanding the haemodynamic effects of NE in the context of the Anrep effect, a physiological response in which the heart compensates for increased afterload by enhancing myocardial contractility and extending the duration of systole.[6,7]

Linking norepinephrine's action to the Anrep effect

We have been investigating the Anrep effect in both physiological[6] and pathological settings,[7] including hypertrophic obstructive cardiomyopathy. Through this, we have characterised its defining features, collectively referred to as the **Anrep triad**, which consists of *three* key haemodynamic responses: (1) **elevated afterload**, indicated by an increase in Ea and left ventricular end-systolic pressure, reflecting the increased workload on the heart; (2) **enhanced myocardial contractility**, demonstrated by a steeper, leftward shift in the

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end-systolic pressure–volume relationship (corresponding to higher Ees) and an increase in the maximum rate of pressure development (dP/dt_{max}); and (3) **prolonged duration of systole**, evidenced by an extended systolic period (dTes), termed Ttot-s by Zhou and colleagues,[5] essential for maintaining SV and cardiac output under increased afterload.

These dynamics are illustrated in Figure 1, which highlights the effects of NE on Ea and Ees as observed by Zhou and colleagues.[5] Although they did not explicitly reference the Anrep effect, the significant increases in Ea, Ees, and Ttot-s observed after NE administration strongly suggest its activation. By raising afterload through α1-mediated vasoconstriction, NE indirectly triggers the Anrep effect, enabling the heart to adapt through enhanced contractility and prolonged systole. This response stabilises SV despite increased vascular resistance.[6]

In septic shock, where systemic vascular resistance is abnormally low, the Anrep effect likely serves a dual purpose: stabilising SV and, in some patients, increasing it.[5] Zhou and colleagues' findings demonstrate this dual role, particularly in SV responders, where elevated Ea and Ees, combined with prolonged systole (Ttot-s), resulted in a net increase in SV.[5] This demonstrates the ability of NE to restore cardiac output from a compromised baseline, reinforcing its influence in managing septic shock complicated by profound vasodilation.

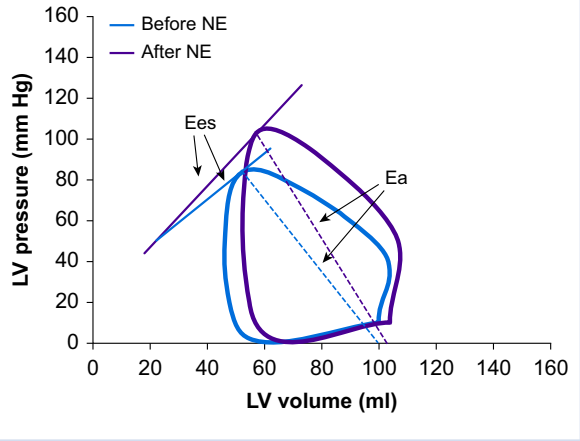

Fig 1. Pressure–volume loops illustrating left ventricular (LV) dynamics before (*blue*) and after (*purple*) norepinephrine (NE) administration in the responder group, reconstructed using average end-diastolic and end-systolic volumes reported by Zhou and colleagues.[5] These volumes correspond closely to maximum and minimum values attributable to the rectangular shape of LV loops in hearts without significant valvular regurgitation. The increase in afterload after NE administration is evident in the steeper slope of the *purple* dashed line (effective arterial elastance, Ea) compared with the *blue* dashed line before NE administration. Concurrently, an increase in myocardial contractility is indicated by the steeper slope of the end-systolic pressure–volume relationship, corresponding to increased end-systolic elastance (Ees), shown by the *purple* solid ascending line compared with the *blue* solid ascending line before NE administration. The early diastolic pressure value was set arbitrarily to 0 mm Hg, and the LV end-diastolic pressure to 10 mm Hg, for illustrative purposes. The loops were recreated using a pressure–volume loop simulator developed by Paul Steendijk (Leiden University Medical Center, The Netherlands).

Differentiating the Anrep effect from other cardiac mechanisms

The Anrep effect operates via mechanisms distinct from slower processes such as the slow force response (SFR; peak force generation in 2–15 min)[8,9] and the Gregg effect (peaking within ~40 s),[10] both of which depend on stretch-activated (preload) ion channels and Ca^{2+} regulation. The SFR enhances force development through calcium influx triggered by myocardial stretch,[8,9] whereas the Gregg effect, also known as the 'coronary perfusion effect', is initiated by increased coronary perfusion.[11,12] This perfusion increases microvascular blood volume, stretching surrounding microvascular structures (e.g. endothelial cells and cardiomyocytes), which activates mechanosensitive Ca^{2+} channels in cardiomyocytes, leading to Ca^{2+} influx and increased cytosolic Ca^{2+} availability. Unlike these preload- and Ca^{2+}-dependent processes, the Anrep effect does not rely on stretch-activated Ca^{2+} influx.[6] It is an afterload-dependent phenomenon driven by the (afterload-sensitive) mechanical recruitment of dormant myosin motors within sarcomeres (~55% of the myosin population remains in a resting state), enabling rapid peak force generation within 10 s, significantly faster than Ca^{2+}-mediated mechanisms such as the SFR and Gregg effect.[6,7] Zhou and colleagues[5] confirmed this distinct mechanism by showing NE-induced improvement in cardiac performance (elevated Ees and prolonged Ttot-s) in response to increased afterload (high Ea), consistent with Anrep activation. These changes occurred independently of heart rate variations, coronary perfusion effects attributed to the Gregg effect, and preload-related mechanisms such as the SFR or the Frank–Starling mechanism.

Heart rate remained constant throughout the study, ruling out the Bowditch effect as a driver of contractility changes.[5] Additionally, although NE-driven improvements in coronary perfusion could theoretically augment force generation through the Gregg effect, such a mechanism likely played a minimal role in septic shock, where coronary perfusion remains within autoregulatory limits.[13] Finally, the absence of significant changes in end-diastolic volume after NE administration in Zhou and colleagues' cohort makes preload-mediated contributions via the SFR or Frank–Starling mechanism unlikely.[5] These observations establish the Anrep effect as a fundamental adaptive mechanism, enabling the heart to maintain circulatory stability during the haemodynamic stress of septic shock.

Afterload responses in septic shock: norepinephrine *vs* phenylephrine

Examining the cardiac and vascular actions of NE and phenylephrine (PE) helps contextualise activation of the Anrep effect in septic shock. Both agents increase afterload via α1-adrenergic receptor-mediated vasoconstriction, yet their effects on SV and cardiac output differ markedly. Although PE stabilises haemodynamics in some patients,[14,15] it is frequently associated with reduced cardiac function and increased mortality.[16–18]

Norepinephrine combines α1-mediated vasoconstriction with myocardial β1-and α1-mediated effects, providing balanced support for cardiovascular stability.[3] In septic shock, however, inotropic activity appears to serve a supplementary role, with the Anrep effect acting as the primary driver of cardiac improvement. This is evidenced by the observation

that, although β1 activity typically shortens systole,[19] Zhou and colleagues[5] observed prolonged systolic ejection time and increased contractility after NE administration, consistent with Anrep effect activation. Furthermore, in conditions resembling heart failure, where β1 signalling can be attenuated, the α1-mediated myocardial effects of NE might take on a compensatory inotropic role.[3]

PE, in contrast, is a pure α1 agonist that relies solely on vascular vasoconstriction to elevate systemic vascular resistance. Unlike NE, the haemodynamic effects of PE are more influenced by patient-specific factors, including preload dependency,[20] baseline heart rate at initiation,[21] and secondary effects such as acidosis and inflammation,[22–24] all of which can exacerbate its negative impact on cardiac function. The distinct pharmacokinetics and pharmacodynamics of PE contribute to its complex haemodynamic profile: a longer half-life (2–3 h)[25] compared with NE (2–6 min),[26] and strong α1 selectivity, often resulting in excessive and sustained afterload elevation.[14] Prolonged afterload can overwhelm compensatory mechanisms, including the Anrep effect, leading to afterload mismatch.[27] In this state, ventricular ejection is impaired, SV decreases, and ventricular dilation occurs as the heart attempts to compensate through preload-dependent mechanisms.[27] Depletion of the 'Anrep reserve' likely contributes to the association of PE with cardiac decompensation,[16] preload dependency,[20] and increased mortality in septic shock.[17,18]

In conclusion, Zhou and colleagues[5] provide a detailed view of how NE influences cardiovascular dynamics in septic shock, offering compelling evidence for activation of the Anrep effect. By identifying three core components of the Anrep triad (elevated afterload, enhanced contractility, and prolonged systole), their work highlights essential adaptive strategies used by the cardiovascular system under severe haemodynamic stress. Recognising the role of the Anrep effect in septic shock could inform more precise haemodynamic management and optimise the therapeutic application of NE in critical care.

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Declarations of interest

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References

1. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; **47**: 1181–247
2. De Backer D, Pinsky M. Norepinephrine improves cardiac function during septic shock, but why? *Br J Anaesth* 2018; **120**: 421–4
3. Endoh M. Cardiac α1-adrenoceptors and inotropy. *Circ Res* 2016; **119**: 587–90
4. Michard F, Biais M, Lobo SM, Futier E. Perioperative hemodynamic management 4.0. *Best Pract Res Clin Anaesthesiol* 2019; **33**: 247–55
5. Zhou X, Pan J, Wang Y, Wang H, Xu Z, Zhuo W. Left ventricular-arterial coupling as a predictor of stroke volume response to norepinephrine in septic shock - a prospective cohort study. *BMC Anesthesiol* 2021; **21**: 56
6. Reil JC, Reil GH, Kovács Á, et al. CaMKII activity contributes to homeometric autoregulation of the heart: a novel mechanism for the Anrep effect. *J Physiol* 2020; **598**: 3129–53
7. Sequeira V, Maack C, Reil GH, Reil JC. Exploring the connection between relaxed myosin states and the Anrep effect. *Circ Res* 2024; **134**: 117–34
8. Dowrick JM, Tran K, Loiselle DS, et al. The slow force response to stretch: controversy and contradictions. *Acta Physiol* 2019; **226**, e13250 (Oxford, England
9. Calaghan S, White E. Activation of Na^+-H^+ exchange and stretch-activated channels underlies the slow inotropic response to stretch in myocytes and muscle from the rat heart. *J Physiol* 2004; **559**: 205–14
10. Gregg DE. Effect of coronary perfusion pressure or coronary flow on oxygen usage of the myocardium. *Circ Res* 1963; **13**: 497–500
11. Lamberts RR, van Rijen MH, Sipkema P, Fransen P, Sys SU, Westerhof N. Increased coronary perfusion augments cardiac contractility in the rat through stretch-activated ion channels. *Am J Physiol Heart Circ Physiol* 2002; **282**: H1334–40
12. Westerhof N, Boer C, Lamberts RR, Sipkema P. Cross-talk between cardiac muscle and coronary vasculature. *Physiol Rev* 2006; **86**: 1263–308
13. Schulz R, Guth BD, Heusch G. No effect of coronary perfusion on regional myocardial function within the autoregulatory range in pigs. Evidence against the Gregg phenomenon. *Circulation* 1991; **83**: 1390–403
14. Kalmar AF, Allaert S, Pletinckx P, et al. Phenylephrine increases cardiac output by raising cardiac preload in patients with anesthesia induced hypotension. *J Clin Monit Comput* 2018; **32**: 969–76
15. Jain G, Singh DK. Comparison of phenylephrine and norepinephrine in the management of dopamine-resistant septic shock. *Indian J Crit Care Med* 2010; **14**: 29–34
16. Larson S, Anderson L, Thomson S. Effect of phenylephrine on cerebral oxygen saturation and cardiac output in adults when used to treat intraoperative hypotension: a systematic review. *JBI Evid Synth* 2021; **19**: 34–58
17. Hawn JM, Bauer SR, Yerke J, et al. Effect of phenylephrine push before continuous infusion norepinephrine in patients with septic shock. *CHEST* 2021; **159**: 1875–83
18. Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA* 2017; **317**: 1433–42

19. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. *Heart Fail Clin* 2009; **5**: 217–28
20. Rebet O, Andremont O, Gérard JL, Fellahi JL, Hanouz JL, Fischer MO. Preload dependency determines the effects of phenylephrine on cardiac output in anaesthetised patients: a prospective observational study. *Eur J Anaesthesiol* 2016; **33**: 638–44
21. Law AC, Bosch NA, Peterson D, Walkey AJ. Comparison of heart rate after phenylephrine vs norepinephrine initiation in patients with septic shock and atrial fibrillation. *CHEST* 2022; **162**: 796–803
22. Morelli A, Lange M, Ertmer C, et al. Short-term effects of phenylephrine on systemic and regional hemodynamics in patients with septic shock: a crossover pilot study. *Shock* 2008; **29**
23. He D, Hu H, Hong L, et al. Norepinephrine combined with phenylephrine versus norepinephrine in patients with septic shock: a retrospective cohort study. *BMC Infect Dis* 2023; **23**: 221
24. Tamion F, Richard V, Sauger F, et al. Gastric mucosal acidosis and cytokine release in patients with septic shock. *Crit Care Med* 2003; **31**: 2137–43
25. Hengstmann JH, Goronzy J. Pharmacokinetics of ^{3}H-phenylephrine in man. *Eur J Clin Pharmacol* 1982; **21**: 335–41
26. Beloeil H, Mazoit JX, Benhamou D, Duranteau J. Norepinephrine kinetics and dynamics in septic shock and trauma patients. *Br J Anaesth* 2005; **95**: 782–8
27. Ross Jr J. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. *Prog Cardiovasc Dis* 1976; **18**: 255–64

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